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CORRESPONDENCE

ETMR-like infantile cerebellar embryonal tumors in the extended morphologic spectrum of *DICER1*-related tumors

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We report for the first time *DICER1* mutations in two infantile cerebellar embryonal tumors not otherwise specified (NOS). Two girls, aged 11 months (case 1) and 8 months (case 2) presented with psychomotor delay. Both MRIs showed a midline posterior fossa tumor (Fig. 1a, b). After gross total resection of the tumor, case 1 was treated with two cycles of etoposide/carboplatin. The controlled MRI showed spinal and leptomeningeal metastasis. After a subtotal resection, case 2 was treated according to institutional protocol for infant with high-risk CNS PNET. MRI showed an increase of the residual mass during maintenance chemotherapy.

Case 1 had histological features of embryonal tumor with multilayered rosettes (ETMR) with an architectural pattern of embryonal tumor with abundant neuropil and true rosettes (Fig. 1f, h, j, l). For case 2, a similar histology was seen but no true rosette was identified (Fig. 1g, i, k, m). In spite of LIN28A immunopositivity, FISH and array CGH failed to detect *C19MC* locus amplification [6]. LIN28A immunopositivity is not exclusive to ETMR, but also occurs in other tumors such as atypical teratoid/rhabdoid tumors (ATRT), ependymomas, and high grade gliomas [6]. ATRT was ruled out by INI1 and BRG1 nuclear immunopositivity in both cases. The genomic profile showed a chromosome 2 gain in both cases (Fig. 1c, d): this feature is observed in about 60% of ETMR [6]. The panel review diagnosis was ETMR NOS for case 1 and CNS embryonal tumor NOS for case 2.

Targeted gene sequencing on tumor DNA identified hotspot mutations corresponding to the RNAse IIIb domain of DICER1 in both tumors, *DICER1* c.5437G>A/p.(Glu1813Lys) and c.5113G>A/p.(Glu1705Lys)

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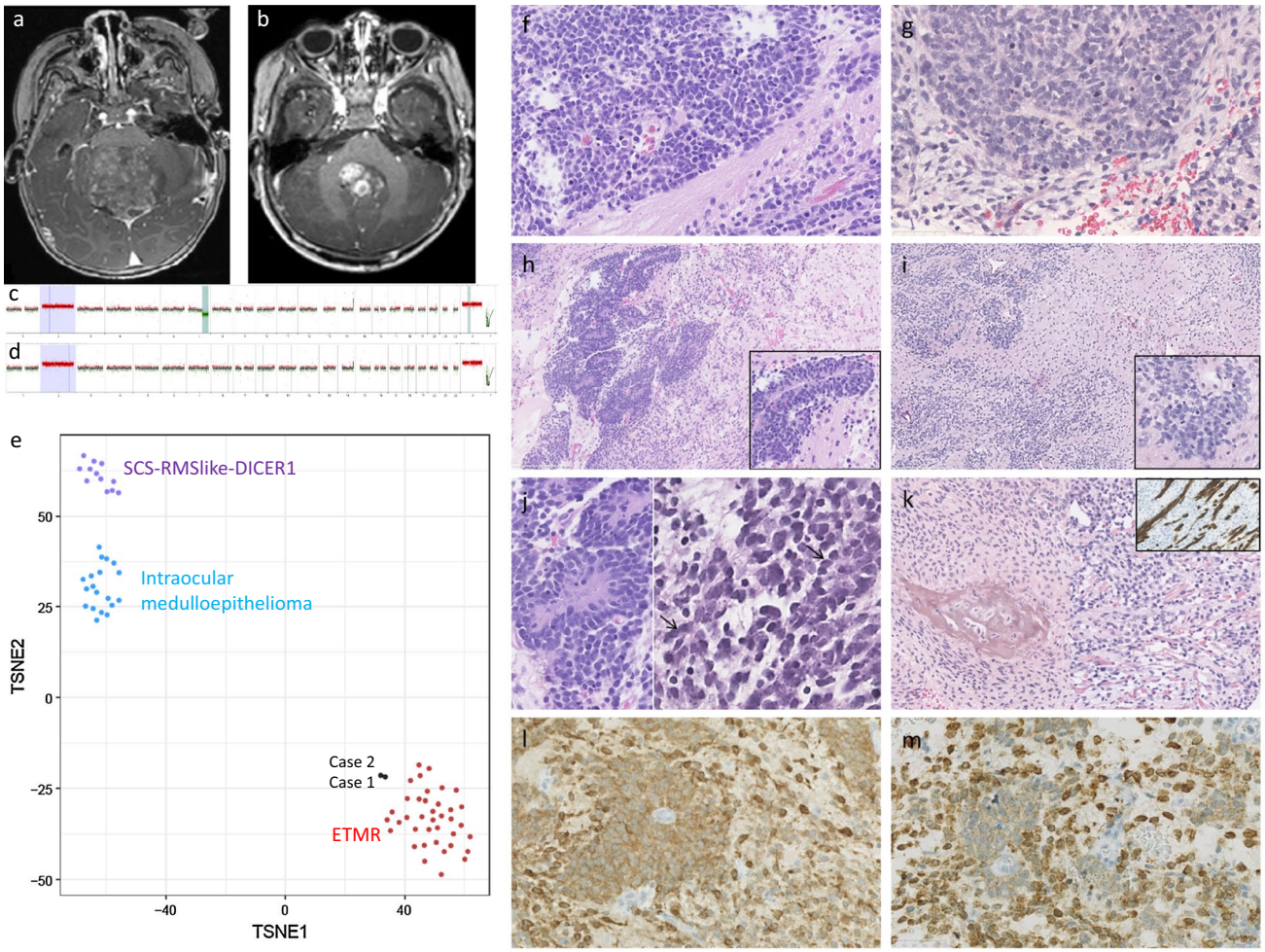

Fig. 1 For case 1 (**a**) and case 2 (**b**), MRI showed a voluminous midline posterior fossa mass, enhancing after contrast injection. Array CGH using agilent 180 k chip showed chromosome 2 gain, 4q (92, 22–93, 43 Mb) segmental gain and 7q (109, 41–158, 58 Mb) segmental loss in case 1 (**c**), and chromosome 2 gain in case 2 (**d**). t-SNE analysis (**e**). H&E showed small undifferentiated monotonous cells with numerous mitoses and apoptotic bodies (**f** case1, g: case 2) and a biphasic histological pattern with areas of small embryonal perivascular cells and neuropil-like areas (**h** case 1, **i** case 2). In case 1, multilayered rosettes (left) and true rosettes (arrows) were observed (**j**). Foci of chondroid (left) and rhabdomyoblastic (right) differentiation were seen in case 2. Detail: desmin immunostaining (**k**). Strong LIN28A immunostaining: case 1 (**l**), case 2 (**m**)

(NM_030621.4) in case 1 and 2, respectively. Germline nonsense pathogenic variants were then retrieved in both children: c.5053C>T/p.(Gln1685*) and c.1200G>A/p.(Trp400*) in case 1 and 2, respectively. Mutations in *DICER1* in other tumor types commonly follow the same pattern of one germline truncating mutation and a somatic missense mutation in the RNase IIIb domain [2, 5, 7]. No feature of *DICER1* syndrome was observed in either family, in accordance with its low penetrance [5]. The tumor from case 1 also had the pathogenic variant c.134C > T/p.(Ser45Phe) in the *CTNNB1* gene. No additional alterations were observed in either tumor on our panel (Supplementary Table 1).

Germline *DICER1* pathogenic variants predispose to a broad spectrum of benign and malignant tumors [5]. Chondroid differentiation is a frequent feature in *DICER1*-associated tumors such as nasal chondromesenchymal hamartoma, rhabdomyosarcoma or anaplastic sarcoma of the kidney [2, 5, 7] and was observed in case 2 (Fig. 1k). Rare CNS embryonal tumors have been described in *DICER1* syndrome including pineoblastoma, pituitary blastoma and ciliary body medulloepithelioma [5]. The posterior fossa localization excluded these diagnoses. Interestingly, medulloepithelioma architectural pattern is one of the three architectural patterns of ETMR. This subtype is LIN28A+ and may not have C19MC alterations. WHO guidelines classify such tumors not as ETMR NOS but as medulloepithelioma, suggesting a different oncogenetic entity. A molecular signature still needs to be found. We hypothesize that DICER1 mutations may have similar effects to *C19MC*

amplification, in at least some medulloepitheliomas, ETMR NOS or embryonal tumors NOS. For case 2, showing a focal muscular differentiation, we considered primary intracranial spindle cell sarcoma with rhabdomyosarcoma-like features, *DICER1* mutant (SCS-RMSlike-DICER1), but smooth muscle actin was detected in all the 17 reported cases and was negative in our case [2]. Moreover, this sarcoma was located supratentorially in 20/22 cases with a median age of 6 years contrasting with our cerebellar infantile case [2].

Using the Heidelberg DNA methylation-based CNS tumor classifier, no class prediction was obtained with the confidence threshold of ≥ 0.9 [1]. The closest entity was ETMR with scores of 0.3 and 0.2 in case 1 and 2, respectively (Methylation data http://www.ncbi.nlm.nih.gov/geo; GSE120122). Using unsupervised t-SNE analysis, both cases were distinct from SCS-RMS-like-DICER1 and intraocular medulloepithelioma and clustered with ETMR (Fig. 1e) [3, 4].

We recommend screening for somatic and germline *DICER1* pathogenic variants in all CNS embryonal tumors NOS, especially if they are LIN28A+, show chondroid differentiation, or are with any tumor of *DICER1* syndrome spectrum. Identification of *DICER1* mutations has implications in terms of genetic counseling and surveillance for patients and families [5].

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